## Appendix I: Background Information

## Neglect Results in Long-Term Cognitive Disability

Unilateral spatial neglect is a lateralized attention disorder characterised by the failure to orient to, attend to, respond to, or report stimuli appearing on the contralesional hemispace, with patients preferring the ipsilesional space (Buxbaum et al., 2004; Vuilleumier, 2013) despite having intact sensory abilities (Howard & Rowe, 2018). Neglect can be present in the personal space, near-extrapersonal space, far-extrapersonal space, or a combination of these (Halligan & Marshall, 1991). The anatomical and structural variability of neglect has been detailed in neuroimaging studies (Committeri et al., 2007; Vuilleumier, 2013), with damage to right-hemisphere lateralized frontoparietal neuroanatomical networks strongly implicated in the pathology (He et al., 2007; Pedrazzini & Ptak, 2020; Wu et al., 2016).

Neglect is commonplace, long-lasting, but highly variable following stroke. Neglect may occur in 43-80% of patients after right-hemispheric stroke and in 20-62% of patients after left-hemispheric stroke (Kaufmann et al., 2020a, 2020b; Harvey et al., 2021; Ringman et al., 2004), all with varying clinical symptoms. Although spontaneous recovery may occur in 20–45% of neglect cases during the acute post-stroke period, (Paolucci et al., 2001), in 40% of cases neglect is still present at least one-year post-stroke (Nijboer et al., 2013). Thus, neglect results in long-term major disability, including mobility problems, restricted activity, and reduced quality of life (Checketts et al., 2020; Conti & Amone, 2016; Wee & Hopman, 2008). The effectiveness of current treatment approaches is uncertain (Longley et al., 2021; Tavaszi et al., 2021; Umeonwuka et al., 2020).

**Classical Clinical Methods Assess Neglect Incompletely**

In clinical settings, neglect is typically assessed using simple pen-and-paper tests such as cancellation tasks (Gauthier et al., 1989; Halligan & Marshall, 1989), clock drawing (Freedman et al., 1994), and line bisection (Albert, 1973), which require patients to approximate the midpoint of lines, draw or copy objects, or cross off targets located among distractors. A non-central or non-symmetrical bias indicates neglect. However, while commonplace and convenient, pen-and-paper tests do not ensure correct identification of moderate neglect, even when several tests are used (Buxbaum et al., 2004, 2012; Harvey et al., 2021). In addition, pen-and-paper tests only allow assessment of neglect of near-extrapersonal space and cannot assess attention in the far-extrapersonal space or in three-dimensional (3D) space (Dvorkin et al., 2012; Ogourtsova et al., 2017). The Catherine Bergego Scale (Azouvi et al., 2002) is an alternative, perhaps more sensitive, systematic, behaviour observation test. Consequently, several researchers have recommended computerised approaches that might detect neglect when classical methods cannot (Bonato et al., 2013; Buxbaum et al., 2012; Ogourtsova et al., 2017), including virtual reality (VR) for neglect assessment (Coyle et al., 2015; Fordell et al., 2011; Pedroli et al., 2015). VR is among the most promising new tools in the development of neuropsychological assessment and rehabilitation applications (Authors own; Pedroli et al., 2015).

**Virtual Reality (VR) is Useful for Cognitive Rehabilitation**

Simulated and immersive technologies, such as VR or augmented reality are often ill defined and confused (Gorman & Gustafsson, 2020). Broadly speaking, VR replaces the perception of reality with a computer stimulation. Modern VR is most commonly a computer-generated, visual simulation of 3D environments that can be interacted with naturalistically, in real-time, using a headset and hand controllers. The headset presents distinct images to the two eyes, producing stereoscopic (i.e., binocular) vision, thereby creating the perception of 3D depth. The headset occludes perception of the external world, and thus the user experiences a surrounding 3D virtual space, a quality of VR termed *immersive*. The controllers act as hands in the virtual world, allowing the user to interact with virtual objects. The key risk of VR is motion sickness, which is minimal on modern high-performance, low latency, computer-driven systems and in scenarios without continuous player translation through space or moving objects (Keshavarz et al., 2011); feelings of motion sickness appear to be low in people with stroke (Laver et al., 2017).

VR is well suited to clinical settings. The 360° immersive environment allows attention to be explored in a naturalistic manner, directly relevant for rehabilitation, in a way traditional 2D computerized tasks and pen-and-paper tasks do not (Harada & Ohyama, 2019). VR allows manipulation of stimuli and scene to build complex environments that allow patients to engage in activities that might be impossible or unsafe for them in the real world (Farrow & Reid, 2004; Kim et al., 2007, 2010). While patients are engaged in rehabilitation in VR, clinicians can synchronously or asynchronously monitor behavioural performance and rehabilitation outcomes, including remotely via telehealth (Burdea, 2003; Morse et al., 2020; Threapleton et al., 2016). VR is readily gamified, which is highly engaging for patients (Pietrzak et al., 2014; Thornton et al., 2005) resulting in greater adherence to treatment (Adlakha et al., 2020). Given sufficient user experience, this may facilitate longer rehabilitation sessions and thus better outcomes (Lohse et al., 2014; Parker et al., 2013, in Huygelier et al., 2021) including physical and mental/psychological outcomes (Freitas et al., 2021; Syed & Kamal, 2021). The recent availability of inexpensive VR technology improves accessibility for clinical uptake (Castelvecchi, 2016) and perceived pitfalls of VR, such as concerns with technological competence have not necessarily played out (Morse et al., 2020). However, research is still in the early stages; evidence of the potential of VR to facilitate meaningful clinical outcomes derives from small studies, of low to moderate quality (Laver et al., 2017) and questions remain over how to increase clinician uptake of technology use (Gorman et al., 2021). Nevertheless, these studies indicate its tolerability and potential utility in people with stroke, with an excellent safety profile.

## VR Can Map Spatial Attention and Attention Problems in Neglect

VR can measure spatial attention and map spatial neglect (Buxbaum et al., 2012; Dvorkin et al., 2012; Harada & Ohyama, 2019; Knobel et al., 2020). In seminal work, Dvorkin et al. (2012) designed a 3D virtual method of mapping the volume of deficit people may experience following stroke. The study included three groups of players; people with stroke and right hemisphere injury and neglect (*n* = 8), people with stroke and right hemisphere injury but without neglect (*n* = 9), and healthy controls (*n* = 9). Players were asked to detect a spherical target presented sequentially at various locations relative to the player’s position on the horizontal or vertical axis or in near or far space. Only those players with neglect showed a pronounced left-side inattention, with response accuracy and reaction time (RT) progressively degraded for targets further from the midline. The authors depicted their results as attention volume maps, showing that VR can map the neglected space.

Knobel et al. (2020) evaluated the feasibility of a simple visual search task for neglect assessment in comparison to pen-and-paper tests. The VR game had players search for targets (20 white spheres) located among distractors (100 white cubes). Players were instructed to find all spheres, as quickly as possible, by touching them with the handheld controller, changing their colour to red. Cubes were to be avoided but would also turn red when touched. The players stopped the task when they stated they had found all objects. Participants reported the VR as usable with minimal adverse effects. Compared with controls, those with neglect identified targets on the right far more than on the left and were slower overall. There was no significant difference in total right-side targets found between the neglect and control groups. The sensitivity of the VR game and pen-and-paper tests to detect neglect were statistically equivalent, and attentional scores derived from the two assessments were highly positively correlated.